1. TITLE PAGE

CLINICAL STUDY REPORT

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Name of Investigational Product	ISIS 721744
Alternative Name	PKK-L_{Rx}
Target	Prekallikrein (PKK)
Indication	Hereditary angioedema (HAE)
Protocol Number	ISIS 721744-CS2
Phase	2a
Study Dates	First Patient Screened: 13 November 2019 First Patient Enrolled (Randomized): 7 January 2020 Last Patient, Last Visit: 15 March 2021
EudraCT Number	2019-001044-22
Clinicaltrials.gov Registration No.	NCT04030598
Study Sponsor	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Phone: (760) 931-9200
Project Director	Ken Newman
Medical Officer	Eugene Schneider
Report Version	1
Date of this Report	15 February 2022

Quality Assurance Statement

This study was performed in accordance with The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6

Confidentiality Statement

2. SYNOPSIS

Name of Sponsor/Company Ionis Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
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Name of Active Ingredient ISIS 721744		

Title of Study

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Investigators Who Enrolled Patients

Jonathan Bernstein, MD; Jason Raasch, MD; William R Lumry, MD; Timothy Craig, DO; Raffi Tachdjian, MD; Danny Michael Cohn; Michael E Manning, MD

Study Centers That Enrolled Patients

Jonathan Bernstein, MD, Bernstein Clinical Research Center, LLC, Cincinnati, OH USA

Jason Raasch, MD, Midwest Immunology Clinic, Plymouth, MN USA

William R Lumry, MD, AARA Research Center, Dallas, TX USA

Timothy Craig, DO, Penn State Health Milton S. Hershey Medical Center, Hershey, PA USA

Raffi Tachdjian, MD, AIRE Medical of Los Angeles, Santa Monica, CA USA

Danny Michael Cohn, Amsterdam UMC, loc. AMC, Amsterdam, The Netherlands

Michael E Manning, MD, Medical Research of Arizona, a division of Allergy, Asthma & Immunology Associates, LTD, Scottsdale, AZ USA

Publication (Citation)

Lauré M. Fijen, M.D., Marc A. Riedl, M.D., Laura Bordone, Ph.D., et al. Inhibition of Prekallikrein for Hereditary Angioedema. N Engl J Med 2022; 386:1026-1033.

Study Duration (Date Range)	**Phase of Development**
7 Jan 2020 to 15 Mar 2021 (last patient completed)	Phase 2a

Objectives

Primary: To evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE) type 1 (HAE 1), HAE type 2 (HAE 2), or HAE with normal C1-inhibitor (C1-INH).

Secondary: To evaluate safety and tolerability of ISIS 721744 in patients with HAE 1/HAE 2 or HAE with normal C1 INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers

Exploratory: To evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide [ASO], including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on relevant biomarkers and clinical outcomes, as appropriate

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Methodology

This study was conducted in 2 parts concurrently with different designs under a master protocol: Part A was randomized, double-blind, and placebo-controlled and Part B was open-label. Patients were allocated into Part A or Part B according to type of HAE, either HAE-1/HAE-2 in Part A or nC1-INH-HAE in Part B. The study visit schedule and procedures were nearly identical in Parts A and B.

In Part A, patients with HAE-1/HAE-2 were to be randomized to subcutaneous (SC) injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, patients with nC1-INH-HAE were to be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of nC1-INH-HAE, enrollment in Part B may have ended early if Study Centers were unable to enroll sufficient patients; this did not affect the completion of Part A.

The length of each patient's participation in the study was approximately 8 months, which included a Screening Period of up to 8 weeks, a 12-week Treatment Period when patients received fixed SC doses of Study Drug every 4 weeks during 4 on-site study visits, and a 4- to 13-week Post-Treatment Period, which was determined by whether a patient enrolled in the ISIS 721744-CS3 open-label extension (OLE) study. Patients returned to the Study Center for post-treatment follow-up visits (or Home Healthcare, if available) at Study Weeks 17, 21, and 26/Early Termination (ET). Alternatively, patients who completed Study Visit Week 17 and met eligibility requirements started the treatment period in the ISIS 721744-CS3 OLE study any time after the Week 17 visit and discontinued participation in the CS2 Post-Treatment Period. For patients not enrolling in the OLE study, the final study visit was the Week 26/ET Visit.

A Data and Safety Monitoring Board (DSMB) reviewed safety, tolerability, and efficacy (as needed) data collected on ISIS 721744 during the study.

Number of Patients (Planned and Analyzed)

Planned enrollment was approximately 18 patients in Part A (12 administered ISIS 721744 and 6 administered placebo) and 6 patients in Part B; 20 patients received Study Drug in Part A (6 placebo, 14 ISIS 721744) and 3 patients received ISIS 721744 in Part B.

Diagnosis and Main Criteria for Inclusion
Inclusion Criteria

1. Patients must have provided written informed consent (signed and dated) and any authorizations required by local law and been able to comply with all study requirements for the duration of the study.
2. Patients must have been aged ≥ 18 years at the time of informed consent.

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Diagnosis and Main Criteria for Inclusion (Continued)
Inclusion Criteria (Continued)

3. Patients must have had a documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or HAE-nC1-INH (for inclusion in Part B) as defined below:
   a. Documented diagnosis of HAE-1/HAE-2 based upon ALL of the following:
      i. Documented clinical history consistent with HAE (subcutaneous [SC] or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018).
      ii. Diagnostic testing results that confirmed HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal could be enrolled if their complement factor C4 (C4) level was below the lower limit of normal (LLN) or if a known pathogenic mutation in the *SERPING1* gene had been demonstrated.
      iii. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range.
   b. Documented diagnosis of HAE-nC1-INH based upon documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018) AND any 1 of the following:
      i. A clinical diagnosis of bradykinin (BK)-mediated angioedema as confirmed with threshold-stimulated kallikrein activity and Investigator-confirmed response to acute use of a BK targeted treatment (icatibant or ecallantide).
      ii. One (1) of the established mutations (c.1032C>A, Thr309Lys; c.1032C>G, Thr309Arg; c.971_1018+24del72*; or c.892_909dup) in the factor XII gene.
      iii. The established mutation in the plasminogen gene (c.988A>G, p.Lys330Glu).
      iv. The established mutation in the angiopoietin-1 gene (c.355G>T, p.A119S).
4. Patients must have:
   a. Experienced a minimum of 2 HAE attacks (assessed by the Angioedema Activity Score [AAS] and confirmed by the Investigator) during the Screening Period.
   b. Completed the AAS questionnaire on a daily basis (minimum of 4 daily assessments per week) for the duration of the Screening Period.
5. Patients must have had access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks.
6. Female patients must have been non-pregnant (and not planning a pregnancy during the study) and non-lactating, and either:
   a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

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Diagnosis and Main Criteria for Inclusion (Continued)
Inclusion Criteria (Continued)
6. (Continued)

b. Postmenopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone [FSH] levels in the postmenopausal range for the laboratory involved).

c. Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post-ovulation methods], declaration of abstinence for the duration of the study, or withdrawal were not acceptable methods of contraception).

d. If engaged in sexual relations of childbearing potential, agreed to use highly effective contraceptive methods (refer to Section 9.4.8) from the time of signing the informed consent form (ICF) until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo).

7. Male patients must have been surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must have agreed to use a highly effective contraceptive method (refer to Section 9.4.8) from the time of signing the ICF until at least 24 weeks after the last dose of Study Drug.

Exclusion Criteria

1. Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening or Study Periods.
2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema.
3. Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks.
4. Any clinically significant abnormalities in screening laboratory values that would have rendered a patient unsuitable for inclusion in the study. The following values were exclusionary:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN).
   b. Bilirubin > 1.5 × ULN unless due to Gilbert's syndrome.
   c. Platelet count < lower limit of normal (LLN).
   d. Estimated glomerular filtration rate (eGFR) < 60 mL/min (as determined by the Cockcroft Gault equation for creatinine clearance).
   e. Activated partial thromboplastin time (aPTT) > 1.5 × ULN
5. Patients with a history of acquired coagulopathies or bleeding diathesis (e.g., thrombocytopenia, disseminated intravascular coagulation, coagulopathy of liver disease, drug-induced platelet dysfunction, hyperfibrinolysis, acquired clotting factor inhibitors) and inherited bleeding disorders (e.g., hemophilia A, hemophilia B, other clotting factor deficiencies, qualitative platelet disorders, inherited thrombocytopenia, vascular abnormalities).

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Exclusion Criteria (Continued)

6. Any clinically significant renal or hepatic diseases.
7. Active infection requiring systemic antiviral or antimicrobial therapy that would not have been completed prior to dosing.
8. Active infection with HIV, hepatitis C, or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who tested positive by serology but negative by RNA may have been allowed in consultation with the Sponsor Medical Monitor.
9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that had been successfully treated.
10. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever was longer, of Screening.
11. Exposure to any of the following medications:
    a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening.
    b. Chronic prophylaxis with lanadelumab within 10 weeks prior to Screening.
    c. Oligonucleotides (including small interfering RNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received.
12. Any condition that, in the opinion of the Investigator, may have compromised the patient's safety or compliance, preclude successful conduct of the study, pr interfere with the interpretation of results.

Test Product, Dose and Mode of Administration, Batch Number

Test Product: ISIS 721744 Injection, 100 mg/mL, 0.8 mL
Dose: 80 mg
Mode of Administration: SC injection
Batch Number: CP721744-001

Duration of Treatment

Patients received doses of Study Drug on Days 1, 29, 57, and 85.

Reference Therapy, Dose and Mode of Administration, Batch Number

Reference Product: Placebo Injection, 1.5 µg/mL riboflavin, 0.8 mL
Mode of Administration: SC injection
Batch Number: CPPLAC-031

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Criteria for Evaluation

Efficacy

The time-normalized number of HAE attacks (per month) from Week 1 to Week 17 (primary) and from Week 5 to Week 17, the time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17, the number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate) by Week 17, the number of HAE attacks requiring acute therapy from Week 5 to Week 17, consumption of on-demand medication at Weeks 9 and 17, and angioedema quality of life (AE-QoL) questionnaire score at Weeks 9 and 17.

Pharmacodynamics

PKK activity, plasma proenzyme activation, and cleaved high molecular weight kininogen (cHK) levels were assessed at Weeks 9 and 17.

Pharmacokinetics

The plasma PK of ISIS 721744 (defined as a total full-length antisense oligonucleotide, including fully conjugated, partially conjugated, and unconjugated ISIS 721744) was assessed.

Safety

Safety assessments were based on treatment-emergent adverse events (TEAEs), clinical laboratory tests (chemistry, hematology, coagulation, complement, and lipid), vital signs assessments, and electrocardiograms (ECGs).

Statistical Methods

The safety population included all enrolled patients who received at least 1 dose of Study Drug, the intent-to-treat (ITT) population included all enrolled or randomized patients, the per-protocol (PP) population included all patients in the ITT population who were treated according to the protocol without any major deviations, and the PK population included all patients who were enrolled and received at least 1 dose of Study Drug and had at least 1 evaluable PK sample.

Efficacy

The primary efficacy endpoint, the time-normalized number of investigator-confirmed HAE attacks per month (defined as 28 days) during the on-treatment period from Week 1 to Week 17 (28 days after last dose administration), was compared between ISIS 721744 and placebo groups in Part A using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model included fixed effect for treatment group (categorical), the time normalized Run in Period attack rate (continuous) as a covariate, and the logarithm of time in month (days from first dose date to 28 days after last dose administration divided by 28) that each patient was observed during the period was used as an offset variable. From this model, the least squares mean rate and standard error for each treatment group, as well as the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals (CIs), were estimated. The p-value of Wald-based chi-square test were also reported. Similar endpoints were analyzed using the same approach.

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Statistical Methods (Continued)
Efficacy (Continued)

For the clinical response rates, the percentage reduction was calculated for each patient as the Treatment Period HAE attack rate from Week 5 to Week 17 minus the Run in Period HAE attack rate divided by the Run in Period HAE attack rate. Risk difference comparing ISIS 721744 to placebo in Part A and corresponding exact 95% CI and the Fisher's Exact test p-value were reported.

The AE-QoL total score and domain scores were analyzed using the same method as described below for the PD variables.

Pharmacodynamics

Change and percent change from Baseline in cHK, plasma proenzyme activation, and PKK levels at each visit during the treatment period were compared between ISIS 721744 80 mg and placebo in Part A using the mixed effects model with repeated measures (MMRM) model. The response variable was the change or percent change from Baseline at post-Baseline visit up to Week 17.

Pharmacokinetics

Non-compartmental PK analysis of ISIS 721744 (total full-length oligonucleotides) was carried out on each individual patient plasma data set. Plasma PK parameters were summarized using descriptive statistics.

Safety

TEAEs were summarized by the number and percentage of patients experiencing each TEAE (coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities [MedDRA], Version 23.0), by relationship to Study Drug, and by severity. The actual results, changes, and percent changes from Baseline were summarized for safety laboratory tests, vital signs, and ECG data.

Sample Size

From historical data, the placebo group was estimated to have 6.8 HAE attacks per 4-month period. Assuming the ISIS 721744 80 mg group would have 2.8 HAE attacks per 4-month period, then with a 0.05 significance level and using Poisson model, the sample size of 18 patients (12 patients administered SC injections of ISIS 721744 80 mg and 6 patients administered placebo) would provide at least 90% power for the primary endpoint, considering a 10% missing data or dropout rate for both active treatment and placebo. The sample size of 18 patients with HAE-1/HAE-2 was also considered sufficient for safety and tolerability evaluation.

There was no statistical rationale for the sample size of 6 patients with HAE-nC1-INH.

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Summary of Results

Demographics and Baseline Characteristics

Among the 20 patients in Part A (6 placebo, 14 ISIS 7721744), demographic characteristics were similar between patients who received placebo and those who received ISIS 721744. Overall, 65% were female, the mean age was 38.5 years (range 21 to 66), 95.0% were white, and the mean body mass index (BMI) was 28.6 kg/m^2 (range 19.6 to 48.1) (Table 7). All 3 patients in Part B were female, the mean age was 34.0 years (range 25 to 40), all were white, and the mean BMI was 38.4 kg/m^2 (range 35.5 to 42). In Part A, 90% of patients had HAE-1 and 10% had HAE-2.

Efficacy

- During the on-treatment period from Week 1 to Week 17, the monthly mean HAE attack rate was 0.23 for the ISIS 721744 group and 2.21 for the placebo group. The percentage difference was -90% (95% CI, -76% to -96%; $p < 0.001$).
- From Week 5 to Week 17, the monthly mean HAE attack rate was 0.07 for the ISIS 721744 group and 2.06 for the placebo group. The percentage difference was-97% (95% CI, -69% to -100%; $p = 0.003$).
- From Week 5 to Week 17, the monthly mean moderate or severe HAE attack rate was 0.05 for the ISIS 721744 group and 1.25 for the placebo group. The percentage difference was -96% (95% CI, -65% to -100%; $p = 0.004$).
- The proportions of patients with a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate from Week 5 to Week 17 were 100%, 92.3%, and 92.3%, respectively, in the ISIS 721744 group vs 33.3%, 16.7%, and 0% in the placebo group ($p \leq 0.004$).
- From Week 5 to Week 17, the mean number of Investigator-confirmed HAE attacks requiring acute therapy was 0.07 in the ISIS 721744 group and 1.40 in the placebo group. The percentage difference was -95% (95% CI, -52% to -99%; $p = 0.009$).
- On-demand medication was used by 85.7% of patients in the ISIS 721744 group and 100% of patients in the placebo group by Week 9.
- Greater improvement was seen with ISIS 721744 vs placebo for the AE-QoL total score and the 4 domain scores. For the total score at Week 17, the mean change from Baseline was -26.85 with ISIS 721744 vs -6.15 with placebo ($p = 0.002$).
- Between Week 5 and Week 17, the percentage of attack-free patients was 92.3% in the ISIS 721744 group vs 0% in the placebo group.
- Although the 3 nC1-INH-HAE patients in Part B were not sufficient to demonstrate efficacy, the reduction in monthly mean attack rate from 4.23 during the Run-in Period to 1.52 from Week 1 to Week 17 (75% reduction) suggests that ISIS 721744 has an effect in this population.

Pharmacodynamics

PKK activity and plasma proenzyme activation were reduced at Week 17 by a mean of 61% and 71% with ISIS 721744 treatment in Part A compared to 3% and 4%, respectively, with placebo. Results in nC1-INH-HAE patients (Part B) were similar to those in C1-INH-HAE patients (Part A).

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Summary of Results (Continued)

Pharmacokinetics

- ISIS 721744 was rapidly absorbed into the systemic circulation with a median T_{max} of 1 hour.
- No accumulation was seen after multiple doses of ISIS 721744, with similar $C_{max,ss}$ and $AUC_{0\text{-}6hr}$ values observed after the first and last dose.
- Exploratory exposure-PD analysis demonstrated a correlation between plasma trough concentrations and reductions in plasma PKK over time.

Safety

- In this study, ISIS 721744 was well-tolerated as multiple SC injections. The overall safety profile of ISIS 721744 in patients with HAE was favorable.
- In Part A, 18 TEAEs were reported for 5 (83.3%) patients and 20 TEAEs were reported for 10 (71.5%) patients. In Part B, 20 TEAEs were reported for 3 (100%) patients. The majority of TEAEs were mild in severity (18 of 18, 100% for placebo; 29 of 40, 72.5% for ISIS 721744 across Parts A and B) and the remainder were moderate. All except 11 TEAEs had resolved.
- No local cutaneous reactions at the injection site or flu-like reactions were reported.
- No patients died in the study, experienced an SAE, or experienced a TEAE leading to discontinuation of Study Drug.
- There were no clinically relevant changes in chemistry, hematology, coagulation, complement, or lipid evaluations, ECGs, or vital signs.
- In patients administered with ISIS 721744, the overall incidence rate was 52.9% (9 of 17 patients). Three ISIS 721744 administered patients (17.6%) had pre-existing antibodies of which all patients were treatment-unaffected. Six ISIS 721744 administered patients (35.3%) had treatment-emergent ADA that were all treatment induced and all persistent in nature.
- Overall, the ADA response was characterized as treatment-induced, early onset, persistent and low titer.
- There was no notable impact of overall or baseline immunogenicity status on measures of pharmacokinetics, pharmacodynamics, or safety

Overall Conclusions

ISIS 721744 significantly reduced the angioedema attack rate and improved quality of life in patients with HAE. Treatment was well tolerated with no severe AEs.

Date of the Report

15 February 2022